FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	112843-034
	U S APPLICATION NO. (IF KNOWN, SEE 37 CFR 10/019848

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/03887	May 2, 2000	April 29, 1999

TITLE OF INVENTION

COMPOSITION FOR AN INFANT FORMULA HAVING A LOW THREONINE CONTENT

APPLICANT(S) FOR DO/EO/US

Kratky, Z., et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☒ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

    Return Receipt Postcard

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/019848 Unknown	PCT/EP00/03887	112843-034

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1040.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$890.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$740.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (c)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	39 - 20 =	19	x $18.00	$342.00
Independent claims	5 - 3 =	2	x $84.00	$168.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$1,400.00
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00
SUBTOTAL =				$1,400.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00
TOTAL NATIONAL FEE =				$1,400.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00
TOTAL FEES ENCLOSED =				$1,400.00
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of **$1,400.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

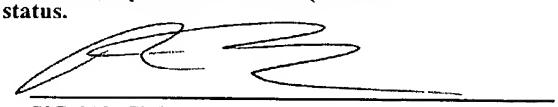
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **02-1818** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Robert M. Barrett (Reg. No. 30,142)
Bell, Boyd & Lloyd LLC
P.O. Box 1135
Chicago, Illinois 60690-1135
Tel: 312/807-4204
Fax: 312/372-2098



SIGNATURE

Robert M. Barrett

NAME

30,142

REGISTRATION NUMBER

October 26, 2001

DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kratky, Z., et al.
Appl. No.: PCT/EP00/03887
Filed: May 2, 2000
Title: COMPOSITION FOR AN INFANT FORMULA HAVING A LOW THREONINE CONTENT
Art Unit: Unassigned
Examiner: Unassigned
Docket No.: 112843-034

Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified patent application as follows:

In the Claims:

Please amend Claims 1-20 as follows:

Claims

1. (Once Amended) A composition for an infant formula comprising a protein source which has a low threonine content and comprising:

a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed;

free arginine;

free histidine; and

a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof.

2. (Once Amended) A composition according to claim 1, wherein the protein source comprises less than about 8g threonine/16g nitrogen.

3. (Once Amended) A composition according to claim 1 which comprises from about 9.0 to about 10.0 w/w% of protein.

4. (Once Amended) A composition according to claim 1, wherein the protein source comprises casein protein.

5. (Once Amended) A composition according to claim 4, wherein the protein source comprises about 6% to about 50% by weight of whey protein and about 20% to about 40% casein protein.

6. (Once Amended) A composition according to claim 1, wherein the protein source is substantially free of lactose.

7. (Once Amended) A composition according to claim 1, wherein the protein source has less than 10% blocked lysine.

8. (Once Amended) A composition according to claim 1, wherein the protein source comprises hydrolyzed protein.

9. (Once Amended) A composition according to claim 8, wherein the protein source comprises about 98.5% to about 97% by weight of hydrolyzed sweet whey protein and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

10. (Once Amended) A composition according to claim 1 which comprises:

about 0.1% to about 3% by weight of arginine;

about 0.2% to about 1% by weight of a component selected from the group consisting of tryptophan and tyrosine; and

about 0.1 to about 1.5% by weight of histidine.

11. (Once Amended) A composition according to claim 1 which comprises a lipid source and a carbohydrate source.

12. (Once Amended) A composition according to claim 11, wherein the lipid source includes medium chain triglycerides.

13. (Once Amended) A composition according to claim 11, wherein the carbohydrate source includes lactose.

14. (Once Amended) An infant formula comprising a protein source having a low threonine content and comprising:

a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed;

a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof;

up to about 1.5% by weight histidine; and

about 0.1% to about 2% by weight arginine.

15. (Once Amended) An infant formula according to claim 14, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

16. (Once Amended) An infant formula according to claim 14, wherein the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

17. (Once Amended) An infant formula according to claim 14, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

18. (Once Amended) A method of producing an infant formula composition comprising the steps of:

blending whey protein and casein protein together with free arginine, free histidine, and a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof, and homogenizing the blended mixture.

19. (Once Amended) A method of providing a medicament to an infant comprising the step of administering to an infant a formula comprising:

a protein source which has a low threonine content and comprising a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed, free arginine, free histidine, a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof, and a medicament.

20. (Once Amended) A method of providing nutrition to an infant comprising the step of administering to an infant a formula comprising:

a protein source which has a low threonine content and comprising a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed, free arginine, free histidine, a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof, and a nutritional agent.

Please add Claims 21-39 as follows:

21. An infant formula according to claim 14, wherein the protein source comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

22. A method according to claim 18, wherein the infant formula comprises less than about 8g threonine/16g nitrogen.

23. A method according to claim 18, wherein the infant formula comprises casein protein.

24. A method according to claim 18, wherein the infant formula is substantially free of lactose.

25. A method according to claim 18, wherein the infant formula comprises:

about 0.1% to about 3% by weight of arginine;

about 0.2% to about 1% by weight of a component selected from the group consisting of tryptophan and tyrosine; and

about 0.1 to about 1.5% by weight of histidine.

26. A method according to claim 18, wherein the infant formula comprises a lipid source and a carbohydrate source.

27. A method according to claim 19, wherein the protein source comprises less than about 8g threonine/16g nitrogen.

28. A method according to claim 19, wherein the protein source comprises casein protein.

29. A method according to claim 19, wherein the protein source is substantially free of lactose.

30. A method according to claim 19, wherein the protein source comprises:

about 0.1% to about 3% by weight of arginine;

about 0.2% to about 1% by weight of a component selected from the group consisting of tryptophan and tyrosine; and

about 0.1 to about 1.5% by weight of histidine.

31. A method according to claim 19, wherein the formula comprises a lipid source and a carbohydrate source.

32. A method according to claim 20, wherein the protein source comprises casein protein.

33. A method according to claim 20, wherein the protein source is substantially free of lactose.

34. A method according to claim 20, wherein the protein source comprises:

about 0.1% to about 3% by weight of arginine;

about 0.2% to about 1% by weight of a component selected from the group consisting of tryptophan and tyrosine; and

about 0.1 to about 1.5% by weight of histidine.

35. A method according to claim 20, wherein the formula comprises a lipid source and a carbohydrate source.

36. A method according to claim 20, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

37. A method according to claim 20, wherein the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

38. A method according to claim 20, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

39. A method according to claim 20, wherein the protein source comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

REMARKS

This Preliminary Amendment is submitted in the above-identified patent application. Pursuant to the Preliminary Amendment Claims 1-20 have been amended and newly submitted Claim 21-39 has been added. This Preliminary Amendment does not add new matter. Further, Applicants note that the Preliminary Amendment is not being made for purposes of narrowing the claims and/or patentability but, merely to comport the claims to U.S. practice and/or to add additional claims. Applicants do not intend to disclaim any subject matter in view of the amendments.

For the foregoing reasons, Applicants respectfully solicit an early and favorable examination of the present patent application.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Versions with Markings to Show Changes Made.**"

Respectfully submitted,

BELL, BOYD & LLOYD LLC

BY _____

Robert M. Barrett
Reg. No. 30,142
P.O. Box 1135
Chicago, Illinois 60690-1135
Phone: (312) 807-4204

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1-20 have been amended as follows:

1. (Once Amended) A composition for an infant formula ~~having~~ comprising a protein source which has a low threonine content and ~~which comprises all of:~~ comprising:

a whey component selected from the group consisting of acid whey protein ~~or~~ and sweet whey protein from which caseino-glyco-macropeptide has been removed; ~~and~~

free arginine; ~~and~~

free histidine; and

a component selected from the group consisting of free tyrosine ~~or~~, free tryptophan ~~or~~, tryptophan rich milk protein ~~or a mixture~~ and mixtures thereof.

2. (Once Amended) A composition according to claim 1, wherein the protein source comprises less than about 8g threonine/16g nitrogen ~~N~~.

3. (Once Amended) A composition according to ~~any preceding~~ claim 1 which comprises from about 9.0 to about 10.0 w/w% of protein.

4. (Once Amended) A composition according to ~~any preceding~~ claim 1, wherein the protein source comprises casein protein.

5. (Once Amended) A composition according to claim 4, wherein the protein source comprises about 6% to about 50% by weight of whey protein and about 20% to about 40% casein protein.

6. (Once Amended) A composition according to ~~any preceding~~ claim 1, wherein the protein source is substantially free of lactose.

7. (Once Amended) A composition according to ~~any preceding~~ claim 1, wherein the protein source has less than 10% blocked lysine.

8. (Once Amended) A composition according to ~~any preceding~~ claim 1, wherein the protein source comprises ~~hydrolysed~~ hydrolyzed protein.

9. (Once Amended) A composition according to claim 8 ~~in which,~~ wherein the protein source comprises about 98.5% to about 97% by weight of ~~hydrolysed~~ hydrolyzed sweet whey protein and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

10. (Once Amended) A composition according to ~~any preceding~~ claim 1 which comprises:

about 0.1% to about 3% by weight of arginine;

about 0.2% to about 1% by weight of a component selected from the group consisting of tryptophan ~~or~~ and tyrosine; and

about 0.1 to about 1.5% by weight of histidine.

11. (Once Amended) A composition according to ~~any preceding~~ claim 1 which comprises a lipid source~~,~~ and a carbohydrate source~~, and a protein source~~.

12. (Once Amended) A composition according to claim 11, wherein the lipid source includes medium chain triglycerides.

13. (Once Amended) A composition according to claim 11 ~~or 12~~, wherein the carbohydrate source includes lactose.

14. (Once Amended) An infant formula ~~which comprises a composition according to any preceding claim wherein the~~ comprising a protein source ~~comprises up to about 0.1%~~ having a low threonine content and comprising:

a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed;

a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof;

up to about 1.5% by weight histidine~~,~~; and

about 0.1% to about ~~0.3%~~ 2% by weight arginine~~,~~. ~~and about 0.3 to about 0.5% by weight tryptophan~~.

15. (Once Amended) An infant formula ~~which comprises a composition~~ according to ~~any one of claims 1 to 13 which~~ claim 14, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

16. (Once Amended) An infant formula ~~which comprises a composition~~ according to ~~any one of claims 1 to 13 which~~ claim 14, wherein the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

17. (Once Amended) An infant formula ~~which comprises a composition according to any one of claims 1 to 13 which~~ claim 14, wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

18. (Once Amended) A method of producing ~~a composition according to any of one of claims 1 to 13 which comprises the step of~~ an infant formula composition comprising the steps of:

blending whey protein and casein protein together with free arginine; free histidine; ~~and tyrosine or~~ and a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein ~~or free tryptophan or a mixture~~ and mixtures thereof, and homogenizing the blended mixture.

19. (Once Amended) ~~Use of a composition according to any one of claims 1 to 13 for the manufacture of~~ A method of providing a medicament ~~or nutritional product for addressing the nutritional needs and providing healthy growth of~~ to an infant comprising the step of administering to an infant a formula comprising:

a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed; free arginine; free histidine; a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof; and a medicament.

20. (Once Amended) A method of ~~addressing the nutritional needs and~~ providing ~~healthy growth of~~ nutrition to an infant ~~which comprises~~ comprising the step of administering ~~an effective amount of a composition according to any one claims 1 to 13~~ to an infant a formula comprising:

a whey component selected from the group consisting of acid whey protein and sweet whey protein from which caseino-glyco-macropeptide has been removed; free arginine; free histidine; a component selected from the group consisting of free tyrosine, free tryptophan, tryptophan rich milk protein and mixtures thereof; and a nutritional agent.

Claims 21-39 have been added.

Composition For An Infant Formula Having a Low Threonine Content

This invention relates to a composition for an infant formula having a low threonine content; a method of producing the composition; use of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant; and a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of the composition.

Within the context of this application the word "comprises" is taken to mean "includes, among other things" and it is not intended to mean "consists of only".

Mother's milk is recommended for all infants. However, in some cases mother's milk is not available and infant formulae must be used. Normal, full-term infants are usually fed cow's-milk-based formulas. These formulas contain a mixture of casein and whey as protein sources and they provide nutrition for infants, however they do not provide a protein concentration and an amino acid profile equivalent to that of mother's milk. In addition these standard formulae are not suitable for pre-term infants and those having adverse reactions to protein in cow's milk formula or to lactose.

An alternatives to cow's milk formula is soy formula; particularly for infants who are lactose intolerant. However, soy is not as good a protein source as cow's milk. Also, infants do not absorb some minerals, such as calcium, as efficiently from soy formulae.

A further alternative formula is based on hydrolysed protein. These formulas are hypoallergenic and have a decreased likelihood of an allergic reaction.

Ideally, to be as close as possible to human milk, the protein in infant formulae may be derived from both whey and casein in an appropriate ratio. However, a problem with conventional formulae having these proteins is that they have a high protein concentration to ensure that the infant gets the necessary amount of all essential amino acids. The protein concentration is higher than the concentration normally found in human milk and it may not be beneficial for an

infant because an infant's metabolism is susceptible to overloading with nitrogen from its protein intake.

To address this problem, formulae having improved amino acid profiles have been suggested, for example those having hydrolysed whey proteins. However, until now there has not been a composition having a protein concentration equivalent to the concentration in human milk and a good amino acid profile.

The present invention addresses the problems set out above.

Accordingly, the invention provides a composition for an infant formula having a low threonine content which comprises all of:

i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and
ii) free arginine; and
iii) free histidine; and
iv) free tyrosine or tryptophan rich milk protein or free tryptophan or a mixture thereof.

In a second aspect the invention provides a method of producing the composition which comprises the step of blending whey protein together with free arginine; free histidine; and free tyrosine or tryptophan rich milk protein, free tryptophan or a mixture thereof and homogenising the blended mixture.

In a third aspect the invention provides use of an embodiment of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant.

In a forth aspect the invention provides a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of an embodiment of the composition.

Preferably the protein source has a threonine content of less than about 8g/16gN, more preferably it is less than about 6g/16gN.

Preferably an embodiment of the composition comprises from about 9.0 to about 10.0 w/w% of protein, more preferably about 9.5% w/w%. This corresponds to about 1.8g protein /100kcal. This provides the advantage of a lower protein concentration relative to known formulae. An advantage provided by this concentration of protein is that it is equivalent to the amount of protein generally present in human milk and it corresponds to the lower limit tolerated by codex alimentarius.

Preferably an embodiment of the composition comprises about 6% to about 50% by weight of whey protein, more preferably about 20% to 40% whey protein, most preferably 30% whey protein.

Preferably the composition also comprises casein protein. An advantage provided by casein is that it has the ability to form curd which enhances the feeling of satiety. Preferably it comprises from about 20% to about 40% casein protein, more preferably about 30%. Preferably, the ratio of whey protein to casein protein is about 60%:about 40% to about 70%:about 30%, most preferably it is about 70%:about 30%.

Preferably the whey protein is acid whey protein or sweet whey protein. In general, acid whey protein is preferred from a nutritional point of view since it has a lower threonine content and this is closer to that of human milk.

Preferably, the sweet whey protein is sweet whey protein from which caseino-glyco-macropeptide has been removed. This provides the advantage of a reduced threonine content and an increased tryptophan content as compared to normal sweet whey and is therefore suitable as a protein source for infants.

Preferably, the whey protein is substantially free of lactose. This has the advantage that the infant formula has reduced levels of lysine blockage. Preferably, the level of lysine blockage is less than 10%.

Preferably an embodiment of the composition comprises protein which is non-hydrolysed. In alternative embodiments it is hydrolysed.

Preferably an embodiment of the composition comprises up to about 4% by weight of arginine; up to about 4% tyrosine or tryptophan; up to about 4% histidine. More preferably an embodiment of the composition comprises about 0.1% to about 3% by weight of arginine; about 0.2% to about 1% tyrosine or tryptophan; about 0.1% to about 2% histidine. More preferably an embodiment of the composition comprises about 0.1% to about 2% by weight of arginine; about 0.2% to about 0.5% tyrosine or tryptophan; about 0.1% to about 1.5% histidine. Suprisingly, it has been found that by supplementing with the free amino acids arginine, tyrosine, and histidine, the protein source has an amino acid profile which is close to that of human milk. This provides the advantage of mimicking the nutritional benefits of natural human milk for addressing the nutritional needs and providing healthy growth of an infant.

Preferably the concentration of tryptophan in the composition is at least about 135mg/g and the concentration of threonine in the composition is less than about 350mg/g. Preferably the threonine concentration corresponds to about 4.9 g per 100g protein to about 5.1g per 100g protein.

Preferably, tryptophan rich milk protein has a level of about 5% or more of amino acids as tryptophan. More preferably it is about 10% or more.

Preferably the free amino acids are in free base form.

Preferably an embodiment of the composition comprises a lipid source, a carbohydrate source, and a protein source. This provides the advantage that the composition is as close as possible in content to mothers milk.

The lipid source may contain medium chain triglycerides.

The carbohydrate source may include lactose. The lactose may be the sole source of carbohydrates.

In one embodiment the composition is suitable for a pre-term infant formula and comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

In an alternative embodiment the composition is suitable for a full-term, hypoallergenic infant formula in which the protein source preferably comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

In an embodiment which comprises hydrolysed protein, the protein source preferably comprises about 98.5% to about 97% by weight of hydrolysed sweet whey and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

An embodiment which comprises hydrolysed protein may be suitable for a pre-term infant formula in which the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine. In this case, the lipid source may include medium chain triglycerides.

An alternative embodiment which comprises hydrolysed protein may be suitable for a full-term, hypoallergenic infant formula in which the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine. The carbohydrate source may include lactose which may be the sole source of carbohydrates.

In an embodiment the invention provides a pre-term infant formula which comprises a lipid source which includes medium chain triglycerides, a carbohydrate source, and a protein source which contains a hydrolysed or non-hydrolysed sweet whey fraction having a level of lysine blockage less than 10%, the protein source having a threonine content of less than about 6 g/16gN.

In a further embodiment, the invention provides a full-term, hypoallergenic infant formula which comprises a lipid source, a carbohydrate source which includes lactose, and a protein source which contains a hydrolysed or non-hydrolysed sweet whey fraction having a level of lysine blockage less than 10%, the protein source having a threonine content of less than about 6 g/16gN.

Embodiments of the invention are now described by way of example.

The invention provides a composition for an infant formula which comprises arginine, tryptophan or tyrosine, histidine and a sweet whey fraction from which caseino-glyco-macropeptide has been removed. The infant formula may be used for pre-term or full-term infants.

An embodiment having hydrolysed protein may be used for pre-term infants or infants susceptible to allergic reactions.

The sweet whey used in the protein source may be obtained from cheese making, particularly the sweet whey obtained after the coagulation of casein by rennet. The sweet whey may then be processed as desired. For example, the sweet whey may be treated to remove minerals (cations, anions), lactose, or any of these substances. The sweet whey may be concentrated as desired. Suitable sweet whey sources are commercially available. It is particularly preferred that the sweet whey is substantially lactose-free.

The sweet whey is then treated to remove caseino-glyco-macropeptide. This may be accomplished by any suitable process. One suitable process is described in European patent application 0880902, the disclosure of which is incorporated by reference. In this process, the pH of the sweet whey is adjusted to 1 to 4.3, if necessary. The sweet whey is then contacted with a weakly anionic resin which is predominantly alkaline until the pH of the sweet whey stabilises at about 4.5 to 5.5. The sweet whey fraction from which the caseino-glyco-macropeptide has been removed, is then collected.

In an embodiment of the composition the whey protein is non-hydrolysed. In an alternative embodiment, the sweet whey fraction is hydrolysed to prevent allergic reactions in infants at risk and to make the protein easier to digest. The hydrolysis process may be carried out as desired and as is known in the art. In general, the whey protein hydrolysate is prepared by enzymatically hydrolysing the sweet whey fraction in one or more steps. For example, for an extensively hydrolysed protein, the sweet whey proteins may be subjected to triple hydrolysis using, for example, Alcalase 2.4L (EC 940459), then Neutrase 0.5L (obtainable from Novo Nordisk Ferment AG) and then pancreatin at 55°C. Alternatively, for a less hydrolysed protein, the sweet whey may be subjected to double hydrolysis using, for example, NOVOZYMES and then pancreatin.

If the sweet whey fraction used is substantially lactose free, it is found that the protein is subjected to much less lysine blockage during the hydrolysis process. This enables the extent of lysine blockage to be reduced from about 15% by weight of total lysine to less than about 10% by weight of lysine; for example about 7% by weight of lysine. This greatly improves the nutritional quality of the protein source.

The free amino acids L-arginine, L-tryptophan or L-tyrosine, and L-histidine are included in the protein source. Preferably, they are in the form of free amino acids and make up about 0.2% to about 3% by weight of the protein source. For example, the free amino acids may make up about 2% to about 2.6% by weight of the protein source.

In particular, for pre-term formulas, histidine preferably provides about 1% to about 1.5% by weight, arginine preferably provides about 0.6% to about 0.9% by weight, and tryptophan or tyrosine preferably provides about 0.3% to about 0.5% by weight, of the protein source. For hypoallergenic formulas, histidine preferably provides about 0.2% to about 0.4% by weight, arginine preferably provides about 1% to about 2% by weight, and tryptophan or tyrosine preferably provides about 0.2% to about 0.4% by weight, of the protein source.

The protein source may include other free amino acids as desired.

The carbohydrate source in the infant formula can be carbohydrate suitable for use in infant formulas. Preferred carbohydrate sources are selected from the group which comprises sucrose, maltodextrin, maltose, lactose, corn syrup, corn syrup solids, rice syrup solids, rice starch, and the like. Preferably, the carbohydrate source includes lactose and maltodextrin. The lactose is preferably free of any allergens. For full term formulas, the carbohydrate source is preferably lactose.

The lipid source may be any lipid or fat which is suitable for use in infant formulas. Preferred lipid sources include milk fat, safflower oil, egg yolk lipid, canola oil, olive oil, coconut oil, palm oil, palm kernel oil, palm olein, soybean oil, sunflower oil, fish oil, and microbial fermentation oil containing long-chain,

polyunsaturated fatty acids. These oils may be in the form of high oleic forms such as high oleic sunflower oil and high oleic safflower oil. The lipid source may also be in the form of fractions derived from these oils such as palm olein, medium chain triglycerides (MCT), and esters of fatty acids such as arachidonic acid, linoleic acid, palmitic acid, stearic acid, docosahexaeonic acid, linolenic acid, oleic acid, lauric acid, capric acid, caprylic acid, caproic acid, and the like.

For pre-term formulas, the lipid source preferably contains medium chain triglycerides; for example in an amount of about 15% to about 35% by weight of the lipid source.

The lipid source preferably has a ratio of n-6 to n-3 fatty acids of about 5:1 to about 15:1; for example about 8:1 to about 10:1.

The infant formula may further comprise ingredients which are designed to meet the nutritional needs of a human infant. In particular, it is preferred that the infant formula is "nutritionally complete"; that is it contains adequate nutrients to sustain healthy human life for extended periods.

The amount of protein per 100 kcal of formula is typically about 1.8g to about 4.5 g; for example about 1.8 g to about 4 g. For full term hypoallergenic formulas, the amount may be about 1.8 g/100 kcal to about 2.5 g/100 kcal. In order to reduce protein loading, the amount is preferably less than about 2 g/100 kcal. For pre-term formulas, the amount may be about 1.8 g/100 kcal to about 4 g/100 kcal.

The amount of lipid source per 100 kcal of formula may be about 3.3 g to about 6.5 g; for example about 4.4 g to about 6.5g. The amount of carbohydrate source per 100 kcal of total formula is typically about 7 g to about 14 g.

When in nutritionally complete form, the infant formula contains all vitamins and minerals understood to be essential in the daily diet and in nutritionally significant amounts. Minimum requirements have been established for certain vitamins and minerals. Examples of minerals, vitamins and other nutrients optionally present in the infant formula include vitamin A, vitamin B_1, vitamin B_2, vitamin B_6, vitamin B_{12}, vitamin E, vitamin K, vitamin C, vitamin D, folic

acid, inositol, niacin, biotin, pantothenic acid, choline, calcium, phosphorous, iodine, iron, magnesium, copper, zinc, manganese, chloride, potassium, sodium, selenium, chromium, molybdenum, taurine, and L-carnitine. Minerals are usually added in salt form. The presence and amounts of specific minerals and other vitamins will vary depending on the intended infant population.

If necessary, the infant formula may contain emulsifiers and stabilisers such as soy lecithin, citric acid esters of mono- and di-glycerides, and the like. This is especially the case if the formula is provided in liquid form.

The infant formula may optionally contain other substances which may have a beneficial effect such as fibres, lactoferrin, nucleotides, nucleosides, and the like.

The infant formula may be prepared in any suitable manner. For example, for an infant formula may be prepared by blending together the protein source, the carbohydrate source, and the fat source in appropriate proportions. If used, the emulsifiers may be included in the blend. The vitamins and minerals may be added at this point but are usually added later to avoid thermal degradation. Any lipophilic vitamins, emulsifiers and the like may be dissolved into the fat source prior to blending. Water, preferably water which has been subjected to reverse osmosis, may then be mixed in to form a liquid mixture.

The liquid mixture may then be thermally treated to reduce bacterial loads. For example, the liquid mixture may be rapidly heated to a temperature in the range of about 80°C to about 110°C for about 5 seconds to about 5 minutes. This may be carried out by steam injection or by heat exchanger; for example a plate heat exchanger.

The liquid mixture may then be cooled to about 60°C to about 85°C; for example by flash cooling. The liquid mixture may then be homogenised; for example in two stages at about 7 MPa to about 40 MPa in the first stage and about 2 MPa to about 14 MPa in the second stage. The homogenised mixture may then be further cooled to add any heat sensitive components; such as vitamins and minerals. The pH and solids content of the homogenised mixture is conveniently standardised at this point.

If it is desired to produce a powdered infant formula, the homogenised mixture is transferred to a suitable drying apparatus such as a spray drier or freeze drier and converted to powder. The powder should have a moisture content of less than about 5% by weight.

If it is desired to produce a liquid infant formula, the homogenised mixture is filled into suitable containers; preferably aseptically. However, the liquid infant formula may also be retorted in the container. Suitable apparatus for carrying out filling of this nature is commercially available. The liquid infant formula may be in the form of a ready to feed formula having a solids content of about 10 to about 14% by weight or may be in the form of a concentrate; usually of solids content of about 20 to about 26% by weight.

Specific examples of the invention are now described for illustration.

Example 1

a) A sweet whey protein concentrate is dissolved in deionised water and the pH is adjusted to 4.25 by contacting the solution with a cation exchange resin (IMAC HP 1100 E, Rohm and Haas). The solution is treated with a weakly anionic resin (IMAC HP 661, Rohm & Haas, which has been regenerated in OH^- form) for about 6 hours at 8°C. Once the pH reaches about 5.25 and does not change, the solution is recovered. Over 85% of the caseino-glyco-macropeptide originally present has been removed from the solution.

b) The solution of step a) is standardised in demineralised water at 55°C. The solution is then heated to 75°C for 20 seconds. The pH of the solution is adjusted to 7.5 by the addition of $Ca(OH)_2$ and a solution of NaOH and KOH.

The reaction mixture is then subjected to microfiltration and ultrafiltration and then dried by lyophilisation and packaged into metal cans. The protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

c) The protein of step b) is combined with 0.72% by weight L-arginine, 0.44% by weight of L-tryptophan, and 1.38% by weight of L-histidine. The mixture is formulated into a powdered infant formula. The infant formula has the following composition:

Component	Amount
Milk SNF	8-10%
Whey protein	6-50%
Alpha-lactalbumin rich whey protein source	0-2%
Arginine	0.1-0.3%
Histidine	0-0.1%
Fat	25-30%
Lactose	10-40%
Vitamins and minerals	To meet regulations

The composition has a protein concentration of 9.5 w/w% or 1.8g protein /100kcal.

Example 2

Step a) is carried out as in Example 1.

b) The solution of step a) is standardised in demineralised water at 55°C. The solution is then heated to 75°C for 20 seconds. The pH of the solution is adjusted to 7.5 by the addition of $Ca(OH)_2$ and a solution of NaOH and KOH. The protein is then hydrolysed using the NOVOZYME enzyme (obtainable from Novo Nordisk Ferment AG). The hydrolysis reaction is continued for 4 hours at 55°C.

An amount of pancreatin is added and the protein is further hydrolysed for 8 hours at 55°C and at a pH of 7.0. The enzymes are then inactivated by heating the reaction mixture to 90°C and holding the mixture at this temperature for about 5 minutes. The reaction mixture is then cooled to 5°C.

The reaction mixture is then subjected to microfiltration and ultrafiltration. The hydrolysed protein is then dried by lyophilisation and packaged into metal cans. The hydrolysed protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

c) The hydrolysed protein of step b) is combined with 0.72% by weight L-arginine, 0.44% by weight of L-tyrosine, and 1.38% by weight of L-histidine. The mixture is formulated into a powdered infant formula. The infant formula has the following composition:

Component	Amount per 100 kcal
Protein	3.6 g
Hydrolysed whey	3.5 g
Free amino acids	0.1 g
Lipids	5.2 g
Medium chain triglycerides	
High oleic sunflower oil	
Soya bean oil	
Palm olein	
Fish oil	
Egg phospholipids	
Carbohydrates	9.9 g
Lactose	2.0 g
Maltodextrin	7.9 g
Vitamins and minerals	To meet regulations

The infant formula is suitable for pre-term infants and has the following amino acid profile:-

Amino Acids	**gAA/16gN**
Aspartic Acid	11.64
Threonine	5.69
Serine	4.79
Glutamic Acid	16.69
Proline	4.90
Glycine	2.16
Alanine	5.37

Cystine	2.69
Valine	5.37
Methionine	2.26
Isoleucine	5.32
Leucine	12.53
Tyrosine	3.42
Phenylalanine	3.95
Lysine	9.58
Histidine	3.37
Arginine	3.42
Tryptophan	2.16

Example 3

a) The solution of step a) of example 1 is standardised in demineralised water at 55°C. The pH is increased from 6.6 to 7.9 by addition of a 20% (weight/volume) aqueous dispersion of $Ca(OH)_2$. The pH is then regulated at 7.3 by compensation with a 2N aqueous solution of KOH.

Pancreatic trypsin is added to initiate hydrolysis and the reaction is continued for 4 hours at 50° C. The hydrolysate is then heated to 90°C by injection of steam and is kept at this temperature for 5 minutes. After cooling to 55° C, the pH is readjusted to 7.3 by automatic compensation with a 2N aqueous solution of KOH. Porcine trypsin is then introduced to initiate second hydrolysis which is continued for 2 hours with automatic compensation of the pH. The hydrolysate is then heat-treated for 10 minutes at 90°C, rapidly cooled and then dried by freeze-drying.

The hydrolysed protein has low levels of lysine blockage. The hydrolysed protein has low levels of lysine blockage with 6.9% blocked lysine and 9% reactive lysine.

b) The hydrolysed protein of step a) is combined with 1.52% by weight L-arginine, 0.3% by weight of L-tyrosine, and 0.3% by weight of L-histidine. The infant formula has the following composition:

Component	Amount per 100 kcal

Protein	1.9 g
Hydrolysed whey	1.86 g
Free amino acids	0.04 g
Lipids	5.1 g
Palm olein	
Coconut oil	
Sunflower oil	
Canola oil	
Egg phospholipids	
Carbohydrates	11.6 g
Lactose	11.6 g
Vitamins and minerals	To meet regulations

The infant formula is suitable for full term, hypoallergenic infants and has a balanced amino acid profile.

Example 4

To compensate for the lesser quality of bovine milk proteins, infant formulae contain more protein than human milk. By improving the quality of the protein it is possible to use less protein. It has now been found that a formula containing modified sweet whey (having caseino-glyco-macropeptide removed) with about 1.83g protein /100kcal results in similar nitrogen retention as a conventional whey-enriched formula with 2.24g protein /100kcal. This has been tested by performing metabolic balance studies with 8 normal infants (2 girls, 6 boys, aged between 39 and 139 days) in a balanced cross-over design. A metabolic balance study (72 hours) was performed with each formula after a washout period of 11 days. The formula having 1.83g protein /100kcal contained modified sweet whey and casein and casein in a ratio of 70:30. The formula having 2.24 g protein /100kcal contained demineralised whey and casein in a ratio of 60:40. In other respects the compositions were similar to commercially available infant formulae.

Results

	Nitrogen (mg/kg/d)

	intake	Ur. Excr.	Fec. Excr.	Retent.
Formula having 1.83g protein /100kcal	349±83	194±21	37±15	117±62
Formula having 2.24 g protein /100kcal	284±54	136±25	31±10	117±63

The data show that adjustment of urinary nitrogen excretion enabled infants to maintain nitrogen retention at identical levels in spite of a substantial difference in intake. Absorption and retention of minerals and fat were similar with both formulae. It was concluded that a modified whey formula with protein-energy ratio 1.83g/100kcal leads to adequate nitrogen and mineral retention in normal infants. Lower urinary nitrogen excretion indicates reduced metabolic load.

Example 5

Commercially available infant formulae contain more protein (>2g/100kcal) than human milk; it is well established that plasma amino acids (AA) of formulae-fed infants deviate from breastfed infants. It has now been found that infants fed two formulae varying in amount and composition of protein (modified whey; 1.83g protein /100kcal; F-1.8 & F-1.8LCP) have AA closer to breast fed infants than infants a whey enriched formula (2.24g protein/100kcal; F-2.2). The 3 formulae were exclusively fed between 6 and 122 days of age. Blood was collected at 30, 61 and 122 days of age. Formula intake and the intervals between last feeding and blood sampling were recorded. AA (ion exchange; tryptophan: HPLC) were measured in plasma of breastfed infants (n=19) and infants fed formula F-1.8 (n=23), F-1.8LCP (n=20), F-2.2 (n=13). Statistical analysis was carried out by Kruskal-Wallis and Mann-Whitney tests. Levels of threonine, the branched chain AA, phenylalanine and lysine in the group fed F-2.2 were significantly higher than in the breastfed group. In the groups fed F-1.8 and F-1.8LCP threonine was close to the breastfed group and the branched-chain AA were not different from the breastfed group. Glycine concentrations win the groups F-1.8 and F-1.8LCP were higher than in the breastfed group. Since the time intervals between feeding and blood sampling did not differ among the groups, the dependence of citruline on protein load with formula (F-2.2, F-1.8, F1.8LCP)

was found to be significant. The higher plasma urea values in the group F-2.2 are therefore due to increased synthesis and not decreased urinary urea excretion. It can be concluded that feeding modified whey formula with 1.8g protein/ 100kcal results in plasma amino acids at 30, 61 and 122 days of age which are close to breastfed infants.

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Claims

1. A composition for an infant formula having a protein source which has a low threonine content and which comprises all of:
   i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and
   ii) free arginine; and
   iii) free histidine; and
   iv) free tyrosine or free tryptophan or tryptophan rich milk protein or a mixture thereof.

2. A composition according to claim 1 wherein the protein source comprises less than about 8g threonine /16g ~~N~~ Nitrogen.

3. A composition according to any preceding claim which comprises from about 9.0 to about 10.0 w/w% of protein.

4. A composition according to any preceding claim wherein the protein source comprises casein protein.

5. A composition according to claim 4 wherein the protein source comprises about 6% to about 50% by weight of whey protein and about 20% to about 40% casein protein.

6. A composition according to any preceding claim wherein the protein source is substantially free of lactose.

7. A composition according to any preceding claim wherein the protein source has less than 10% blocked lysine.

8. A composition according to any preceding claim wherein the protein source comprises hydrolysed protein.

9. A composition according to claim 8 in which the protein source comprises about 98.5% to about 97% by weight of hydrolysed sweet whey protein and about 1.5% to about 3% by weight of arginine, tyrosine, and histidine.

10. A composition according to any preceding claim which comprises about 0.1% to about 3% by weight of arginine; about 0.2% to about 1% by weight of tryptophan or tyrosine; and about 0.1 to about 1.5% by weight of histidine.

11. A composition according to any preceding claim which comprises a lipid source, a carbohydrate source, and a protein source.

12. A composition according to claim 11 wherein the lipid source includes medium chain triglycerides.

13. A composition according to claim 11 or 12 wherein the carbohydrate source includes lactose.

14. An infant formula which comprises a composition according to any preceding claim wherein the protein source comprises up to about 0.1% by weight histidine, about 0.1% to about 0.3% by weight arginine, and about 0.3 to about 0.5% by weight tryptophan.

15. An infant formula which comprises a composition according to any one of claims 1 to 13 which wherein the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tryptophan.

16. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 1% to about 1.5% by weight histidine, about 0.6% to about 0.9% by weight arginine, and about 0.3% to about 0.5% by weight tyrosine.

17. An infant formula which comprises a composition according to any one of claims 1 to 13 which the protein source comprises about 0.2% to about 0.4% by weight histidine, about 1% to about 2% by weight arginine, and about 0.2% to about 0.4% by weight tyrosine.

18. A method of producing a composition according to any one of claims 1 to 13 which comprises the step of blending whey protein and casein protein

together with free arginine; free histidine; and tyrosine or tryptophan rich milk protein or free tryptophan or a mixture thereof and homogenising the blended mixture.

19. Use of a composition according to any one of claims 1 to 13 ~~in~~ for the manufacture of a medicament or nutritional product for addressing addressing the nutritional needs and providing healthy growth of an infant.

20. A method of addressing ~~addressing~~ the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of a composition according to any one of claims 1 to 13.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/11990 A1

(51) International Patent Classification[7]: A23L 1/29, 1/305, 1/30, 1/09

(21) International Application Number: PCT/EP00/03887

(22) International Filing Date: 2 May 2000 (02.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99108405.4 29 April 1999 (29.04.1999) EP
9923048.4 29 September 1999 (29.09.1999) GB

(71) Applicant *(for all designated States except US)*: **SOCIETE DES PRODUITS NESTLE S.A.** [CH/CH], P.O. Box 353, CH-1800 Vevey (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KRATKY, Zdenek** [CZ/CH]; Au Rattalez, CH-1613 Maracon (CH). **MAIRE, Jean-Claude** [CH/CH]; 1, ch. de Rueyres, CH-1092 Belmont S/Lausanne (CH). **BALLEVRE, Olivier** [FR/CH], Rte de Cojonnex 16B, CH-1000 Lausanne 25 (CH). **HASCHKE, Ferdinand** [AT/CH]; Route de Lavaux 254, CH-1095 Lutry (CH). **JOST, Rolf** [CH/CH]; Bolligenstrasse 71, CH-3065 Bolligen (CH). **KUSLYS, Martinas** [CH/CH], Moosackerweg 2B, CH-3506 Grosshoechstetten (CH) **MEISTER, Niklaus** [CH/CH], Moschbergweg 20, CH-3506 Grosshoechstetten (CH). **SECRETIN, Marie-Christine** [FR/CH]; Ch. du Dévin 11, Les Chevalleyres, CH-1807 Blonay (CH)

(74) Agent: **LOCK, Graham**; Avenue Nestlé 55, CH-1800 Vevey (CH).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/11990 A1

(54) Title: COMPOSITION FOR AN INFANT FORMULA HAVING A LOW THREONINE CONTENT

(57) Abstract: A composition for an infant formula which comprises a low threonine content; a method of producing the composition; use of the composition in the manufacture of a medicament or nutritional product for addressing the nutritional needs and providing healthy growth of an infant; and a method of addressing the nutritional needs and providing healthy growth of an infant which comprises administering an effective amount of the composition. A preferred embodiment of the composition comprises all of: i) acid whey protein or sweet whey protein from which caseino-glyco-macropeptide has been removed; and ii) free arginine; and iii) free histidine; and iv) free tyrosine or free tryptophan or tryptophan rich milk protein or a mixture thereof.

80305/US
6536/US

Docket No.
112843-034

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

COMPOSITION FOR AN INFANT FORMULA HAVING A LOW THREONINE CONTENT

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **2 May 2000** as United States Application No. or PCT International Application Number **PCT/EP00/03887**

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
99108405.4	**Europe**	**29 April 1999**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
9923048.4	**Great Britain**	**29 September 1999**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

29174
PATENT & TRADEMARK OFFICE

Send Correspondence to: **Robert M. Barrett**
Bell, Boyd & Lloyd LLC
P.O. Box 1135
Chicago, IL 60690-1135

Direct Telephone Calls to: *(name and telephone number)*
Robert M. Barrett (312) 807-4204

1-00

Full name of sole or first inventor **Zdenek Kratky**	
Sole or first inventor's signature	Zdenek Kratky October 29, 2001 Date
Residence **Maracon, Switzerland** CH-1X	
Citizenship **~~Czechoslovakia~~** USA 1.10.1991	
Post Office Address **Au Rattalez**	
CH-1613 Maracon, Switzerland	

2-00

Full name of second inventor, if any **Jean-Claude Maire**	
Second inventor's signature	J Maire Date November 1st, 2001
Residence **Belmont S/Lausanne, Switzerland** CH-1X	
Citizenship **Switzerland**	
Post Office Address **1,ch. de Rueyres**	
CH-1092 Belmont S/Lausanne, Switzerland	

3-00

Full name of third inventor, if any
Olivier Ballevre

Third inventor's signature

Date 1/11/01

Residence
Lausanne 25, Switzerland CHX

Citizenship
France

Post Office Address
Rte de Cojonnex 16B

CH-1000 Lausanne 25, Switzerland

4-00

Full name of fourth inventor, if any
Ferdinand Haschke

Fourth inventor's signature

Date 8.11.01

Residence
Lausanne, Switzerland CHX

Citizenship
Austria

Post Office Address
Route de Lavaux 254

CH-1095 Lutry, Switzerland

5-00

Full name of fifth inventor, if any
Rolf Jost

Fifth inventor's signature

Date 8.11.01

Residence
Bolligen, Switzerland CHX

Citizenship
Switzerland

Post Office Address
Bolligenstrasse 71

CH-3065 Bolligen, Switzerland

6-00

Full name of sixth inventor, if any
Martinas Kuslys

Sixth inventor's signature

Date 8.11.01

Residence
Grosshoechstetten, Switzerland CHX

Citizenship
Switzerland

Post Office Address
Moosackerweg 2B

CH-3506 Grosshoechstetten, Switzerland

over

7 - 00

Full name of seventh inventor, if any
Niklaus Meister

Seventh inventor's signature

Date 8/1

Residence
Grosshoechstetten, Switzerland CHX

Citizenship
Switzerland

Post Office Address
Moschbergweg 20

CH-3506 Grosshoechstetten, Switzerland

8 - 00

Full name of eighth inventor, if
Marie-Christine Secretin

Eighth inventor's signature

Date 16.11.01

Residence
Blonay, Switzerland CHX

Citizenship
France

Post Office Address
Ch. du Devin 11, Les Chevalleyres

CH-1807 Bloney, Switzerland

Full name of ninth inventor, if any

Ninth inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of tenth inventor, if any

Tenth inventor's signature

Date

Residence

Citizenship

Post Office Address